REMARKS

The present application was filed in the USPTO in 2002 more than 8 years ago. The first office action was issued by the Examiner in October 2004. There have been two in-person interviews, an RCE and an Appeal brief filed December 23, 2009. On April 29, 2010, the Examiner sent an office action raising a new grounds of rejection of all the claims based on obviousness resulting from the combination of two references, the Koster et al. reference which described DNA amplification using archael enzymes (developed and patented by Applicants) and the Reid et al. reference which compared certain polymerases, which are outside the scope of the present claims. It is well known that references should be enabled in order to serve as prior art. The Examiner's analysis of what constitutes enablement for a person of ordinary skill in the art in the prior art appears to have little relation to the Examiner's statements on enablement for a person of ordinary skill in the art in the §112 rejection.

Rejection under 35 U.S.C. §103

The Examiner states the following:

> The expectation of success is high as everything that is required to perform the made obvious method is taught by the references of Koster et al. and Reid et al... (p. 8 of the office action dated 4/29/10)

Applicants respectfully assert that this statement is incorrect.

In the first place, Koster et al. is irrelevant since it is well known that vent polymerase has been used in amplification and the claimed method is concerned with the use of acyclonucleotides for chain termination.

The introduction of the Reid et al. reference as suggesting to a person of ordinary skill in the art that acyclonucleotides would be better than dideoxynucleotides for chain termination in the presence of the claimed polymerases is simply incorrect. In fact, Reid et al. teach the opposite. Applicant respectfully requests that the Examiner review the present application on page 6 which states:

> Evidence has been proffered that the Family B herpes virus type 2 (HSV-2) and human cytomegalovirus (HCMV) DNA polymerases have a preference for insertion of acyclo-GTP over ddGTP (Reid, et al., J. Biol. Chem. 263: 3898-3904 (1988)). The same report also indicates a strong preference by human DNA polymerase alpha (also a Family B DNA polymerase) for insertion of ddGTP over acyclo-GTP (emphasis added).

Reid et al. explored various antiviral agents with respect to polymerase-dependent replication including dhpG, acyclovir, dideoxy and arabinosyl nucleoside triphosphates. Reid et al. concluded that there were three contrasting behaviors.

> First, extension behavior with araNTP, second insertion/extension behavior with dhpGTP and third the relative preference for insertion of ddGTP versus acyGTP (emphasis added).

Both Applicants and Reid et al. reveal that different classes of polymerases differ in their ability to incorporate different modified nucleotides. Neither Herpes Type 2 nor human cytomegalovirus studied by Reid et al. are within the scope of the present definition of the polymerases in the claimed invention.

Given the opposite results obtained for the two classes of polymerase examined by Reid et al., there is no basis in the Reid et al. reference to extrapolate the observations to the present claimed class of polymerases which differs from the two classes described by Reid et al.

It is clear from Table 3 of the present application that Herpes Type 2 and human cytomegalovirus lie outside the definition of the polymerases defined in the present claims which state:

> ... at least 30% overall identity with that of the polypeptide encoded by SEQ ID NO:4, and further includes a 15 amino-acid motif that is identical to one of SEQ ID NOs 5-22 or contains up to 3 amino acid substitutions as compared with the one of SEQ ID NO 5-22.

This description and the claimed structure are not arbitrary. The polymerases that fall within the definition are highly conserved Family B archeaon DNA polymerases (page 18 of the specification), which form a class of enzymes that are understandably distinct from other Type B polymerases such as viral polymerases. The conserved motif is not a random motif but is described structurally and functionally in the application in great detail on pages 10-15.

As such, the degree of sequence similarity particularly in conserved motifs is predictive of the degree to which the proteins will behave similarly in both physical properties and catalytic function.

In view of the above, the Examiner is requested to reverse the rejection of the claims as obvious with respect to the cited references.

Rejection of claims 32-42 under 35 U.S.C. §112 first paragraph

The Examiner has maintained his rejections of claims 32-42 under 35 U.S.C. §112 1st paragraph as non-enabled but has withdrawn his rejection relating to lack of description. Much has been written in the prosecution over the previous 6 years with respect to enablement. There is a fundamental disagreement over a value judgment, namely, whether a person of skill in the art could practice the claimed invention. Dr. Jack's declaration asserts that the ordinary person would be able to. The examiner asserts that they could not.

Enablement of the claimed invention relies on reviewing the specification supporting the claims. The specification provides a comprehensive description of the class of polymerases defined in the claims, an assay (Example 1) now incorporated into the amended claim 32 and their use with a specific modified nucleotide, namely, an acyclonucleotide.

The Dr. Jack declaration states that the claimed method of using acyclonucleotides is applicable for a highly conserved group of polymerases that has been structurally and functionally defined in the claims and in the specification. The Dr. Jack declaration is supported by extensive documentation in the application and in the figures.

The Dr. Jack declaration provided under oath and dated May 4, 2006 states the following in paragraph 8:

> I assert that the combination of the high degree of homogeneity in DNA and amino acid sequences of archeaon DNA polymerases plus the structural evidence that modification of specific amino acids alters enzyme specificity would be sufficient to assure a person of ordinary skill in the art that the class of polymerases as defined above will interact with acyclonucleotide substrates as shown in the above application.

Despite this sworn statement and the associated published references on the structural homogeneity of archeal polymerases, the Examiner states that there is insufficient guidance to justify the "extreme breadth of these DNA polymerases" (archael polymerases). The 15 amino acid motif is insufficient to provide direction and guidance with respect to the vast number of DNA polymerases encompassed by these structural limitations.

The Examiner states that "without sufficient guidance, determination of those DNA polymerases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue."

No factual evidence was provided to support the Examiner's contention as required in order to refute the Dr. Jack declaration.

The Examiner has not provided any objective evidence to support his statement concerning "the extreme breadth of the claimed genus".

The Examiner repeats the statement of Applicants that all tested DNA polymerases having the motif have the activity and DNA polymerases lacking the activity do not.

The Examiner simply disagrees. But on what basis - why?

Applicants' confusion as to the basis of the Examiner's rejection in view of all the arguments and evidence presented over the last 6 years of prosecution and in view of the low threshold of a person of ordinary skill in the art evidenced by the §103 rejection herein is further increased in light of the claims issued by the present Examiner in US 7,541,170. This patent, filed a few months earlier than the present application, utilized a portion of an archael polymerase fused to another polymerase. The appeal filed in response to an enablement rejection by the Examiner stated "structural information is used to select amino acid residues for substitution that can be reasonably expected to preserve DNA binding function and accordingly the ability to influence polymerase processivity". It is noted that the claims that were allowed were of significantly greater breadth than the present claims since they were limited in one domain only to 75% sequence identity while

defining a functionality of enhancing processivity with no definition of the second domain. (Appeal Brief, Wang Application No. 09/870,353, now U.S. Patent No. 7,541,170.

The Examiner requests that the Applicants limit the claimed invention to the examples. To do so would be to invite competitors to freely copy the claimed invention after reading the enabled description and instead utilize any enzyme with the specified structure other than those particular recited in the specific examples. For this reason, Applicants are unable to accept this limitation because it would deprive the Applicant of a limited monopoly for the disclosed and enabled invention.

In order to expedite the prosecution, Applicants have amended claim 32 by introducing an assay described in Example 1 by which to further characterize the polymerase functionally. No new subject matter has been introduced. The content of page 8, line 7 of the published PCT application referenced by the Examiner is not suited as a claim limitation.

Applicants request that the rejection be reversed.

CONCLUSION

Applicants respectfully submit that this case is in condition for immediate allowance. Early and favorable consideration leading to prompt issuance of this Application is earnestly solicited.

Applicants petition for a three-month extension of time and authorize that the fee of $555 be charged to Deposit Account No. 14-0740. Please charge Deposit Account No. 14-0740 for any deficiencies.

Respectfully submitted,
NEW ENGLAND BIOLABS, INC.

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